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Risk Factors for Readmission after Allogeneic Hematopoietic Stem Cell Transplantation and Impact on Overall Survival

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Patients treated with allogeneic hematopoietic stem cell transplantation (HSCT) are presumed to be at high risk for hospital readmission. The objective of this study was to identify the incidence and associated risk factors for readmissions in allogeneic HSCT patients and to evaluate the effect of readmissions on overall survival. In this retrospective review, we included 1141 HSCT patients (503 patients receiving a myeloablative [MAC] HSCT and 638 a reduced-intensity conditioning [RIC] HSCT). We measured rates of readmission at 30 days after discharge from HSCT and by day +100 after HSCT. Reasons for readmission, risk factors for readmission, and effect on overall survival were assessed. In the MAC group, 130 of 459 (28.3%) patients were readmitted within 30 days of discharge and 195 of 456 (42.8%) patients by day 100. In the RIC group, 105 of 600 (17.5%) patients were readmitted within 30 days of discharge and 185 of 595 (31.1%) patients by day 100. There were significantly more readmissions in the MAC group at both the 30-day ($P < .001$) and day +100 time points ($P < .001$). The most frequent reason for readmission was infection (28.2% in MAC group, 27.3% in RIC group). The occurrence of infection during the index admission was the only risk factor significant in both groups at both time points in the multivariable regression analysis. Readmission was significantly associated with decreased overall survival in both groups and at both time points. MAC patients are readmitted significantly more than RIC patients. Infection is the most common cause of readmission after HSCT and the occurrence of infection during the index transplantation admission is a significant risk factor for readmission. Readmission within 30 days of discharge and by day +100 after transplantation was a significant risk factor for a lower 5-year overall survival rate in both groups.

INTRODUCTION

Hospital readmissions shortly after index hospitalization increases health care costs. Recent studies suggest that approximately 20% or greater of Medicare patients are readmitted within 30 days of discharge, with the vast majority of these readmissions being unplanned [1-3]. Much of the earlier research on 30-day readmissions in the United States focused on pneumonia, heart failure, and acute myocardial infarction, with studies demonstrating marked heterogeneity in readmission rates across the country [4-7]. There is also evidence that readmission rates vary by race and site of care [8]. Readmissions are felt to be an indicator of failure of care transition. They are also costly, with Medicare spending an estimated 17 billion dollars annually on readmissions within 30 days of discharge [1]. Likewise, 30-day readmissions have become an important quality metric in health care and the Affordable Care Act has enacted the Hospital Readmissions Reduction Program [9]. Although current measures exclude oncology patients, the program will likely continue to expand to include these patients in the future. This potentially has significant implications for oncology, as very little is known about the readmission profiles of cancer patients. Gaining a better understanding of the risk factors for readmissions among the oncology population has the potential to result in substantial health care cost savings as well as enhance quality of life for oncology patients.

Hematopoietic stem cell transplantation (HSCT) readmission rates are especially poorly described. Although HSCT is potentially curative for patients with otherwise incurable hematologic malignancies, the procedure is associated with significant post-transplantation morbidity and mortality. HSCT results in defects in innate and adaptive immunity that increase the risk of opportunistic infections. Moreover, there is an intrinsic risk of graft-versus-host disease (GVHD) and relapse. These vulnerabilities increase the risk of readmission

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in the weeks to months after HSCT. The timing of these vulnerabilities is often affected by the type of conditioning regimen used. Myeloablative conditioning (MAC) regimens cause irreversible cytopenias. Nonmyeloablative (NMA) conditioning regimens cause minimal cytopenias. Reduced-intensity conditioning (RIC), an approach that has become more common over the years, features cytopenias of variable duration.

Although HSCT is a relatively uncommon procedure in general, a 2009 Agency for Healthcare Research and Quality report noted that it was among the top 10 procedures with the greatest increase in hospital costs from 2004 to 2007, with a growth rate of 84.9% from $694 million to $1.3 billion, related to both costs and the number of hospitalizations [10]. There has been a significant increase in the number of transplantations performed both domestically and worldwide over the past several years [11]. Transplantation rates are expected to continue to increase with anticipated improvements in transplantation technology and supportive care practices, in addition to the emergence of new indications and alternative graft sources [12,13]. Given the high-risk nature of these immunocompromised patients, the threshold to readmit is relatively lower and many quality metrics cannot be easily generalized to this population. The purpose of our study was to identify the incidence of and reasons for readmission in transplantation patients, as well as to explore associated risk factors for readmission and the impact of readmission on overall survival (OS).

METHODS

Patients and Setting

A retrospective review of patients receiving MAC, RIC, or NMA conditioning HSCT at Dana Farber/Brigham and Women's Hospital between January 1, 2005 and December 31, 2010 was performed. For the purpose of this analysis, all patients receiving an NMA conditioning regimen were analyzed as part of the RIC group. Conditioning regimen intensity was defined according to Center for International Blood and Marrow Transplant Research criteria [14]. Medical records of 1141 HSCT patients were reviewed, with 503 patients receiving a MAC transplant and 638 patients receiving a RIC transplant. The most common MAC regimen used was cyclophosphamide with total body irradiation (88% of patients) and the most common RIC regimen used was fludarabine/busulfan (89% of patients). Recipients of cord blood units and patients who previously received an allogeneic transplant were excluded before the analysis. All patients received their stem cells while admitted to an inpatient bone marrow transplantation unit. Per institutional guidelines, the RIC transplantation patients were discharged on day +1 to 2, unless complications occurred. The MAC transplantation patients remained hospitalized until their absolute neutrophil count recovered above 500 cells/uL for 2 days, they were afebrile, and they were able to manage independently at home. All patients received discharge medication teaching from an oncology pharmacist, registered nurse, or oncology-trained physician assistant and discharge precautions teaching from an oncology registered nurse. Follow-up appointments were arranged by the inpatient team for within 5 days of discharge.

Measurements

The 30-day after discharge and the day 100 after transplantation, a key time point in transplantation, readmission rates were examined. Information on hospital readmissions was collected retrospectively from the physician documentation in the electronic chart, including readmissions outside of the home institution when available. We analyzed age, gender, race, ethnicity, marital status, distance traveled, median income for home zip code, insurance type, primary caregiver, disease type, disease risk index [15], prior treatment with radiation therapy, prior autologous transplantation (for RIC only), disease status at time of transplantation, donor type, stem cell product type, use of total body irradiation during conditioning (for MAC only), documented infection during index HSCT admission, grade II to IV GVHD [16] during index HSCT admission, hepatic veno-occlusive disease (for MAC only) during index HSCT admission, and length of stay for index HSCT admission. Myeloid malignancies included acute myelogenous leukemia, myelodysplastic syndromes, myeloproliferative neoplasms, and chronic myelogenous leukemia. Lymphoid malignancies included acute lymphoblastic leukemia, biphenotypic leukemia, lymphomas, multiple myeloma, and plasma cell leukemia. Other conditions included aplastic anemia and other benign hematologic disorders. Infections were defined as any documented bacterial, viral, or fungal infections with isolation of a specific microorganism. The only exception was pneumonia, for which the presence of both clinical and radiologic findings of pneumonia was accepted as an infection.

Statistical Analysis

To identify the risk factors for 30-day or day +100 readmission rates, patients who died during their index transplantation admission or before the corresponding time points without readmission were excluded (44 in MAC group, 38 in RIC group). An additional 2 patients who stayed in the hospital for more than 100 days during their transplantation admission were also excluded from the day +100 readmission analysis. Potential risk factors were compared between patients readmitted and those not admitted using the Fisher's exact test or the Wilcoxon rank-sum test [17,18]. Factors with a univariate *P* value less than or equal to .20 were further evaluated in the multivariable logistic model. To evaluate the impact of 30-day or day +100 readmission on survival, a landmark analysis was performed among the patients who survived beyond the corresponding time points. Survival curves were estimated using the Kaplan-Meier method and were tested between groups using the log-rank test [19,20]. The effect of readmission on OS was also evaluated in a Cox regression model after adjusting for age, donor type, and the disease risk index [21].

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RESULTS

In the MAC group, 130 of 459 (28.3%) patients were readmitted within 30 days of discharge and 195 of 456 (42.8%) patients were readmitted by day 100 after transplantation. In the RIC group, 105 of 600 (17.5%) patients were readmitted within 30 days of discharge and 185 of 595 (31.1%) patients were readmitted by day 100 after transplantation. As shown in Table 1, there were significantly more readmissions in the MAC group at both the 30-day ($P < .001$) and day +100 time points ($P < .001$).

Taking into account all readmissions, in both groups the most frequent reasons for readmission were infection (28.2% in MAC group, 27.3% in RIC group), fever without a source (19.2% in MAC group, 19.9% in RIC group), and GVHD (18.0% in MAC group, 15.9% in RIC group). Other less common reasons included veno-occlusive disease, gastrointestinal diagnoses, acute kidney injury, and neurologic diagnoses. Of the 34 RIC patients with an initial readmission reason of fever without a source at the 30-day readmission time point, 15 of the patients (44%) were neutropenic at the time of readmission. Baseline characteristics with univariate analysis of both the readmitted and the not-readmitted subsets for the MAC and RIC groups at each readmission time point of interest are summarized in Tables 2 and 3, respectively, and are further discussed below. Results of the multivariate logistic regression model of risk factors for each group and time point are summarized in Table 4 and are further discussed below.

MAC: 30-Day Readmission Risk Factors

Compared with those in the MAC group who was not readmitted by 30 days after discharge, the readmitted group

Table 1
Readmission Rates

Conditioning	30-Day Readmission Rate	Day +100 Readmission Rate
MAC	130 of 459 (28.3%)	195 of 456 (42.8%)
RIC	105 of 600 (17.5%)	185 of 595 (31.1%)
P Value	<.001	<.001

Table 2
MAC Patient Characteristics

Variable	Readmitted by 30 Days (n = 130)	Not Readmitted by 30 Days (n = 329)	*P* Value	Readmitted by Day +100 (n = 195)	Not Readmitted by Day +100 (n = 261)	*P* Value
Sociodemographic variables						
Age, median (range)	45.5 (18-60)	45 (19-59)	.66	45 (18-60)	45 (19-59)	.80
Male	62 (48)	181 (55)	.18	104 (53)	137 (52)	.92
Race						
White	125 (96)	321 (98)	.49	189 (97)	254 (97)	.59
Black	1 (1)	3 (1)		1 (1)	3 (1)	
Other	34 (3)	5 (2)		5 (2)	4 (2)	
Ethnicity						
Non-Hispanic	122 (94)	321 (98)	.09	183 (94)	257 (98)	.01
Hispanic or Latino	8 (6)	8 (2)		12 (6)	4 (2)	
Married	74 (57)	227 (69)	.02	118 (61)	182 (70)	.05
Lives ≤ 60 miles away	65 (50)	137 (42)	.12	93 (48)	109 (42)	.18
Zip code median income ≤ 60K	86 (66)	218 (66)	.91	125 (64)	176 (67)	.61
Primary insurance						
Medicaid	15 (12)	27 (8)	.53	23 (12)	18 (7)	.18
Medicare	4 (3)	10 (3)		6 (3)	8 (3)	
Private	111 (85)	291 (88)		165 (85)	235 (90)	
Other	0 (0)	1 (0)		1 (1)	0 (0)	
Primary caregiver						
Spouse or significant other	82 (63)	255 (78)	.01	132 (68)	204 (78)	.08
Parents	25 (19)	40 (12)		35 (18)	29 (11)	
Siblings	8 (6)	17 (5)		12 (6)	12 (5)	
Children	2 (2)	7 (2)		3 (2)	6 (2)	
Other	13 (10)	10 (3)		13 (7)	10 (4)	
Disease variables						
Disease						
Myeloid	83 (64)	230 (70)	.43	122 (63)	189 (72)	.03
Lymphoid	45 (35)	94 (29)		71 (36)	67 (26)	
Other*	2 (2)	5 (2)		2 (1)	5 (2)	
DRI						
Low risk or n/a	15 (12)	42 (13)	.28	23 (12)	30 (11)	.26
Intermediate	74 (57)	155 (47)		99 (51)	128 (49)	
High	30 (23)	100 (30)		54 (28)	76 (29)	
Very high	7 (5)	10 (3)		11 (6)	5 (2)	
Unknown	4 (3)	22 (7)		8 (4)	18 (7)	
Prior XRT	7 (5)	21 (6)	.83	9 (5)	19 (7)	.32
In CR at HSCT	75 (58)	208 (63)	.34	115 (59)	166 (64)	.38
Transplantation variables						
HSCT type			.02			.10
MRD	47 (36)	162 (49)		78 (40)	130 (50)	
MURD	71 (55)	150 (46)		102 (52)	117 (45)	
MMRD/MMURD	12 (9)	17 (6)		15 (8)	14 (6)	
Donor, unrelated	80 (62)	165 (50)	.03	114 (58)	129 (49)	.06
Product						
PBSC	119 (92)	304 (92)	.85	178 (91)	242 (93)	.60
BM or PBSC+BM	11 (8)	25 (8)		17 (9)	19 (7)	
TBI-containing prep	117 (90)	304 (92)	.45	180 (92)	238 (91)	.73
Documented infection during HSCT	79 (61)	125 (38)	<.001	112 (57)	91 (35)	<.001
GVHD II-IV during HSCT	20 (15)	23 (7)	.01	29 (15)	12 (5)	<.001
VOD during HSCT	8 (6)	12 (4)	.31	12 (6)	7 (3)	.10
Length of stay for HSCT, d	27 (21-98)	26 (11-104)	.004	27 (20-98)	25 (11-81)	.003
Days to first readmission	11.5 (1-30)	–		40 (17-100)	–	

DRI indicates disease risk index; XRT, radiation therapy; CR, complete response/remission; MRD, matched related donor; MURD, matched unrelated donor; MMRD, mismatched related donor; MMURD, mismatched unrelated donor; PBSC, peripheral blood stem cells; BM, bone marrow; TBI, total body irradiation; VOD, veno-occlusive disease.
Values in brackets correspond to percentage rounded to nearest whole number or range for median values.
* Other includes aplastic anemia and other nonmalignant conditions.

had significantly more patients of single marital status (43% versus 31%, $P = .02$), with a caregiver other than a spouse or significant other (37% versus 22%, $P = .01$), with an unrelated donor (62% versus 50%, $P = .03$), with documented infection during HSCT admission (61% versus 38%, $P < .001$), and with acute GVHD during HSCT admission (15% versus 7%, $P = .01$), and the readmitted patients had longer initial hospital stays for the transplantation (median days of stay 27 versus 26, $P = .004$). A multivariate logistic regression model suggested that the significant risk factors for readmission by 30 days after discharge in the MAC group were having a child or nonrelative as a primary caregiver versus a spouse or significant other (odds ratio [OR], 3.10; $P = .04$), the occurrence of acute GVHD during index transplantation admission (OR, 2.60; $P = .007$), and the occurrence of an infection during the index admission (OR, 2.51; $P < .001$).

MAC: Day +100 Readmission Risk Factors

Of the 195 MAC patients readmitted by day 100 after transplantation, 145 had 1 readmission, 39 had 2 readmissions, 9 had 3 readmissions, and 2 had 4 readmissions during the study period. Compared with those in the MAC

Table 3
RIC Patient Characteristics

Variable	Readmitted by 30 Days (n = 105)	Not Readmitted by 30 Days (n = 495)	*P* Value	Readmitted by Day +100 (n = 185)	Not Readmitted by Day +100 (n = 410)	*P* Value
Sociodemographic variables						
Age, median, yr	59 (24-73)	58 (17-74)	.02	60 (19-73)	57 (17-74)	<.001
Male	68 (65)	300 (61)	.44	118 (64)	249 (61)	.52
Race						.10
White	99 (94)	482 (97)	.17	175 (95)	401 (98)	
Black	3 (3)	7 (1)		6 (3)	4 (1)	
Other	3 (3)	6 (1)		4 (2)	5 (1)	
Ethnicity						.21
Non-Hispanic	103 (98)	479 (97)	.75	182 (98)	395 (96)	
Hispanic or Latino	2 (2)	16 (3)		3 (2)	15 (4)	
Married	81 (77)	352 (71)	.23	139 (75)	293 (71)	.37
Lives ≤ 60 miles away	46 (44)	221 (45)	.83	79 (43)	188 (46)	.48
Zip code median income ≤ 60K	64 (61)	335 (68)	.17	124 (67)	271 (66)	.85
Primary insurance						.04
Medicaid	11 (10)	32 (6)	.12	16 (9)	25 (6)	
Medicare	21 (20)	68 (14)		37 (20)	52 (13)	
Private	73 (70)	392 (79)		132 (71)	330 (80)	
Other	0 (0)	3 (1)		0 (0)	3 (1)	
Primary caregiver						
Spouse or significant other	86 (82)	380 (77)	.43	151 (82)	313 (76)	.50
Parents	3 (3)	27 (5)		8 (4)	22 (5)	
Siblings	3 (3)	30 (6)		7 (4)	26 (6)	
Children	7 (7)	30 (6)		13 (7)	22 (5)	
Other	6 (6)	28 (6)		6 (3)	27 (7)	
Disease variables						
Disease						.007
Myeloid	55 (52)	216 (44)	.002	97 (52)	170 (41)	
Lymphoid	39 (37)	243 (49)		73 (39)	208 (51)	
>1 Malignancy	9 (9)	11 (2)		10 (5)	10 (2)	
Other*	2 (2)	25 (5)		5 (3)	22 (5)	
DRI						
Low risk or n/a	26 (25)	127 (26)	.10	44 (24)	109 (26)	.15
Intermediate	37 (35)	234 (47)		75 (41)	193 (47)	
High	24 (23)	98 (20)		42 (23)	80 (20)	
Very high	5 (5)	10 (2)		7 (4)	6 (1)	
Unknown	13 (12)	26 (5)		17 (9)	22 (5)	
Prior XRT	18 (17)	72 (15)	.55	29 (16)	61 (15)	.81
Prior Auto SCT	17 (16)	121 (24)	.10	31 (17)	105 (26)	.02
In CR at HSCT	30 (29)	210 (42)	.004	56 (30)	181 (44)	<.001
Transplantation variables						
HSCT type			.16			.09
MRD	29 (28)	176 (36)		53 (29)	151 (37)	
MURD	63 (60)	279 (56)		111 (60)	227 (55)	
MMRD/MMURD	13 (12)	40 (8)		21 (11)	32 (8)	
Donor, unrelated	76 (72)	316 (63)	.11	132 (71)	256 (62)	.04
Product			.20			.20
PBSC	103 (98)	470 (95)		180 (97)	388 (95)	
BM or PBSC+BM	2 (2)	25 (5)		5 (3)	22 (5)	
Documented infection during HSCT	26 (25)	29 (6)	<.001	36 (19)	19 (5)	<.001
GVHD II-IV during HSCT	3 (3)	3 (1)	.07	3 (2)	3 (1)	.38
Length of stay for HSCT, d	8 (6-49)	8 (6-51)	.008	8 (6-49)	8 (6-51)	.08
Days to readmission	11 (1-30)	–		29 (3-99)	–	

Values in brackets correspond to percentage rounded to nearest whole number or range for median values.
* Other includes aplastic anemia and other non-malignant conditions.

group who were not readmitted by 100 days after transplantation, the readmitted group had significantly more patients of Hispanic or Latino ethnicity (6% versus 2%, $P = .01$), with a lymphoid malignancy (36% versus 26%, $P = .03$) compared with a myeloid malignancy, with documented infection during HSCT admission (57% versus 35%, $P < .001$), and with acute GVHD during HSCT admission (15% versus 5%, $P < .001$), and the readmitted patients had longer initial hospital stays for the transplantation (median days of stay 27 versus 25, $P = .003$). A multivariate logistic regression model suggested that the significant risk factors for readmission by day +100 in the MAC group after transplantation were having a lymphoid malignancy versus a myeloid malignancy (OR, 1.77; $P = .01$), the occurrence of acute GVHD during index HSCT admission (OR, 3.98; $P < .001$), and the occurrence of infection during index HSCT admission (OR, 2.47; $P < .001$).

RIC: 30-Day Readmission Risk Factors

Compared with those in the RIC group who were not readmitted by 30 days after discharge, the readmitted group was older (median age 59 versus 58, $P = .02$), had significantly more patients with myeloid malignancies compared with lymphoid malignancies (55% versus 44%, $P = .002$), significantly more patients with active disease at the time of transplantation (71% versus 58%, $P = .004$), higher rates of documented infection during HSCT admission (25% versus

Table 4
Risk Factors for Readmission: Logistic Regression Analysis

Effect	OR	95% CI	*P* Value
MAC: Model for 30-day readmission			
Gender			
Male versus female	.70	.47-1.10	.10
Caregiver			
Children/other versus spouse/ significant other	3.10	1.04-9.00	.04
Parents versus spouse/significant other	2.46	.96-6.33	.06
Sibling versus spouse/significant other	2.21	.69-7.03	.18
Marital status			
Married versus single	1.36	.59-3.12	.47
Distance from DFCI			
≤60 miles versus >60 miles	1.38	.89-2.13	.15
Donor type			
MMRD/MMURD versus MRD	1.91	.80-4.54	.14
Donor type			
MURD versus MRD	1.49	.94-2.36	.09
Acute GVHD			
Present during index HSCT admission versus not	2.60	1.30-5.19	.007
Infection			
Present during index HSCT admission versus not	2.51	1.62-3.89	<.001
RIC: Model for 30 day readmission			
Age			
≥58 versus <58	1.19	.67-2.10	.56
Median income by zip code			
>60K versus < or equal to 60K	1.44	.86-2.42	.17
Insurance			
Medicaid versus private	2.48	.96-5.85	.06
Medicare and self-pay versus private	1.23	.61-2.46	.57
Disease type			
Lymphoid versus myeloid	.67	.35-1.30	.24
>1 Malignancy versus myeloid	3.30	1.04-10.50	.04
DRI			
Very high risk versus low risk	.95	.23-4.00	.95
High risk versus low risk	.63	.27-1.46	.28
Intermediate risk versus low risk	.62	.31-1.24	.18
Prior auto SCT			
Yes versus no	.87	.42-1.78	.70
CR at transplantation			
Active disease or not	1.99	1.13-3.51	.02
Donor type			
MMRD/MMURD versus MRD	1.74	.73-4.15	.21
MURD versus MRD	1.32	.74-2.34	.35
Infection			
Present during index HSCT admission versus not	6.09	3.06-12.14	<.001
MA: Model for day +100 readmission			
Ethnicity			
Non-Hispanic versus Hispanic or Latino	.29	.08-.10	.05
Marital status			
Married versus single	1.22	.57-2.60	.61
Caregiver			
Children/other versus spouse/ significant other	1.64	.57-4.68	.36
Parents versus spouse/significant other	2.19	.90-5.29	.08
Siblings versus spouse/significant other	1.70	.55-5.25	.36
Insurance			
Medicaid versus private	1.35	.64-2.88	.43
Medicare and self-pay versus private	.81	.25-2.64	.73
Distance from DFCI			
≤60 miles versus >60 miles	1.16	.77-1.75	.48
Disease type			
Lymphoid versus myeloid	1.77	1.15-2.75	.01
Other versus myeloid	.61	.10-3.67	.59
Donor type			
MMRD/MMURD versus MRD	1.25	.53-2.97	.61
MURD versus MRD	1.34	.88-2.04	.18
Acute GVHD			
Present during index HSCT admission versus not	3.98	1.86-8.51	<.001
VOD			
Yes versus no	1.93	.69-5.41	.21
Infection			
Present during index HSCT admission versus not	2.47	1.65-3.71	<.001
RIC: Model for day +100 readmission			
Age			
≥58 versus <58	1.47	.92-2.34	.10
Insurance			
Medicaid versus private	2.06	.91-4.68	.08
Insurance			
Medicare and self-pay versus private	1.41	.81-2.46	.23
Prior auto SCT			
Yes versus no	.88	.50-1.55	.65
Disease type			
Lymphoid versus myeloid	.64	.38-1.07	.09
>1 Malignancy versus myeloid	1.59	.54-4.72	.40
DRI			
Very high risk versus low risk	1.40	.39-5.04	.61
High risk versus low risk	.73	.37-1.43	.36
Intermediate risk versus low risk	.84	.49-1.46	.54
CR at transplantation			
Active disease or not	2.19	1.41-3.42	<.001
Donor type			
MMRD/MMURD versus MRD	1.46	.71-3.00	.30
MURD versus MRD	1.22	.78-1.91	.38
Infection during HSCT			
Yes versus no	5.57	2.76-11.25	<.001

CI indicates confidence interval; DFCI, Dana-Farber Cancer Institute.

6%, $P < .001$), and longer initial hospital stays for the transplantation ($P = .008$). A multivariate logistic regression model suggested that the significant risk factors for readmission by 30 days after discharge in the RIC group were having greater than 1 hematologic malignancy versus a single myeloid malignancy (OR, 3.30; $P = .04$), having active disease at the time of transplantation (OR, 1.99; $P = .02$), and the occurrence of infection during index HSCT admission (OR, 6.09; $P < .001$).

RIC: Day +100 Readmission Risk Factors

Of the 185 RIC patients readmitted by day 100 after transplantation, 127 had 1 readmission, 37 had 2 readmissions, 14 had 3 readmissions, and 7 had 4 readmissions during the study period. Compared with those in the RIC group who were not readmitted by 100 days after transplantation, the readmitted group was older (median age 60 versus 57, $P < .001$), had significantly fewer patients with private insurance (71% versus 80%, $P = .04$), significantly more patients with a myeloid malignancy (52% versus 41%, $P = .007$), significantly fewer patients with prior autologous HSCT (17% versus 26%, $P = .02$), significantly more patients with active disease at the time of transplantation (70% versus 56%, $P < .001$), more with an unrelated donor (71% versus 62%, $P = .04$), and more with documented infection during HSCT admission (19% versus 5%, $P < .001$). A multivariate logistic regression model suggested that the significant risk factors for readmission by day +100 after transplantation in the RIC group were having active disease at the time of transplantation (OR, 2.19; $P < .001$) and the occurrence of infection during index HSCT admission (OR, 5.09; $P < .001$).

Effect of Readmission on OS

In a landmark analysis of patients who survived beyond the studied time points, the 5-year OS for those readmitted within 30 days of discharge from the index HSCT in the MAC

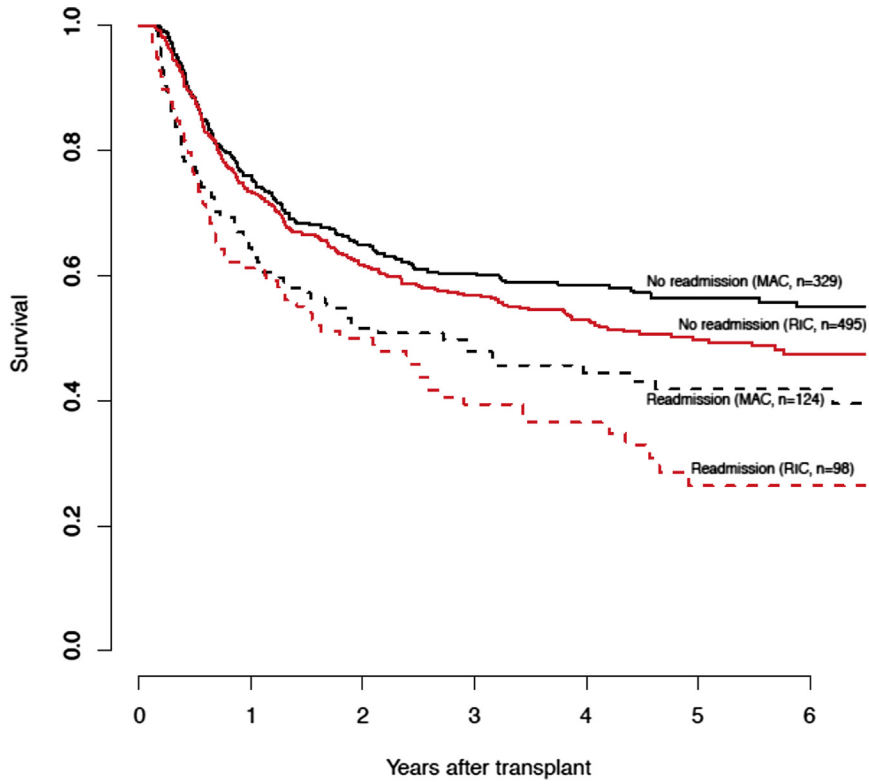

Figure 1. Overall survival by readmission within 30 days of discharge.

group was 42% compared with 56% among patients not readmitted ($P = .003$) (Figure 1). Similarly, OS in the RIC group was 26% compared with 50% ($P < .001$) (Figure 1).

The 5-year OS for those readmitted by day 100 after HSCT in the MAC group was 48% compared with 60% among patients not readmitted ($P = .007$) and in the RIC group was 26% compared with 57% ($P < .001$) (Figure 2). After adjusting for age, donor type, and the disease risk index [15], a multivariable Cox regression analysis confirmed that readmission by 30 days after discharge was significantly associated with decreased OS, with a hazard ratio (HR) (readmitted versus not readmitted) of 1.58 in the MAC group ($P = .002$) and 1.68 in the RIC group ($P < .001$). Similarly, readmission by day +100 after transplantation was significantly associated with decreased survival in the MAC group (HR, 1.46; $P = .009$) and in the RIC group (HR, 2.31; $P < .001$).

DISCUSSION

In this analysis, patients who received MAC were readmitted significantly more frequently than patients who received RIC at 30 days after discharge and at day +100 after transplantation. Reasons for readmission were similar among both groups, with infection and fever without a source being the 2 most common reasons. Among both groups and both time points, infection during the index transplantation admission was found to be a significant risk factor for readmission. The occurrence of acute GVHD during the index transplantation admission was a significant predictor of readmission at both time points in the MAC group in the univariate analysis and for predicting 30-day readmission in the multivariate analysis. Lacking evidence of active disease at the time of transplantation was protective against readmission in the RIC group at both time points in both the univariate and multivariate analysis. Readmission within 30 days of discharge or by day +100 after transplantation was significantly associated with a lower 5-year OS rate in both the RIC and MAC groups, based on univariate and multivariate analysis.

A study at the Cleveland Clinic looking at 30-day readmissions among 618 adult patients after myeloablative allogeneic HSCT demonstrated a readmission rate of 39% [22]. Although this is higher than our reported rate of 28.3%, the Cleveland study took place over a 20-year period dating back to 1990 and the supportive care of transplantation patients and the stringency of matching criteria have evolved in that time. Similar to our study, infection and fever with or without a source were the most common reasons for readmission. Our study also confirmed the negative impact on survival seen in the Cleveland study with MAC patients readmitted by 30 days after discharge. In a multivariable analysis, the Cleveland study showed total body irradiation–based preparative regimens and infection during index admission to both be significant predictors of 30-day readmission for MAC patients. Our study confirmed the significance of infection during index admission.

A limitation of the study is the generalizability to patients treated at other cancer centers, as there is variation in the management of RIC transplantation patients across different institutions. The procedure can be performed entirely as an outpatient and, likewise, the first admission after the procedure would not be considered a readmission at such centers, though it is essentially equivalent as such admissions are presumably due to an adverse effect related to transplantation. In other centers, RIC patients may remain inpatients for the entire process, including conditioning, stem cell infusion, and recovery of the neutrophil count, if applicable, which would likely result in less readmission as a function of a longer index length of stay. Some centers,

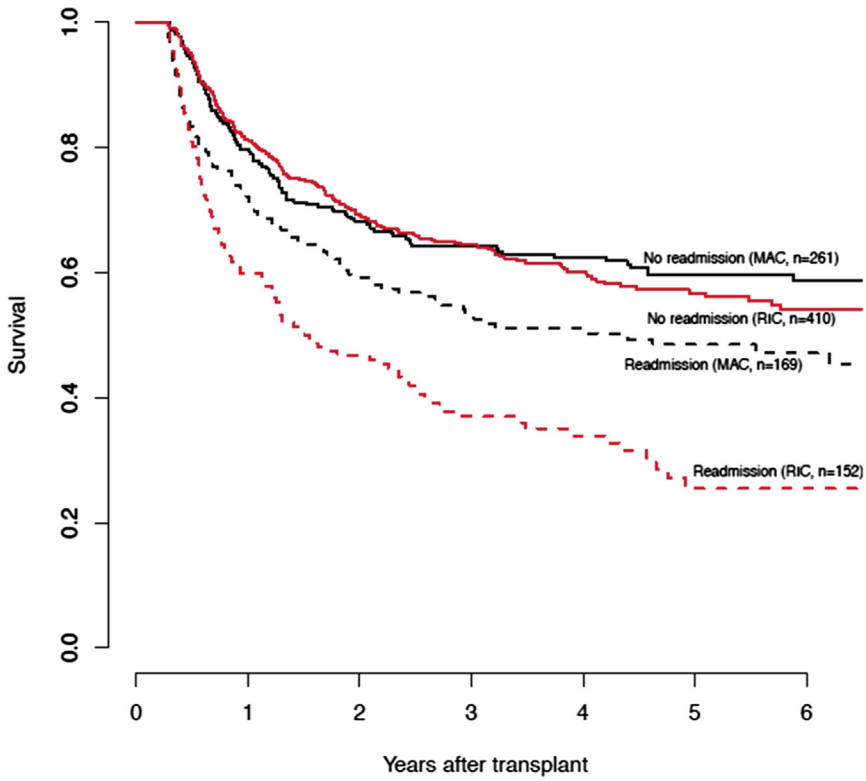

Figure 2. Overall survival by readmission by day +100 after HSCT.

including our center, typically discharge RIC patients on day +1 to 2 after stem cell infusion. A 30-day readmissions study based on 91 patients undergoing transplantation with varying conditioning intensities at West Virginia University between August 2007 and December 2012 demonstrated a 30-day readmission rate of 38% [23]. The only significant risk factor found was documented infection during the index hospitalization. A cost analysis showed that 30-day readmissions significantly increased 100-day post-transplantation hospital charges, supporting its use as a quality measure. At their center, all patients admitted for RIC transplantation remain as inpatients until their neutrophils have engrafted. More research is needed to understand how variations in the management of RIC transplantations affects readmissions and cost.

Other limitations of our study include it being a single-institution, retrospective analysis. However, the high volume at our center allowed us to limit the study to recent years, which more accurately reflects the current state of transplantation. Some of the variables studied were likely limited by small sample size. Additionally, a small number of readmissions to outside institutions were likely missed because of insufficient documentation. Lastly, our current analysis did not include cord blood transplantations. Preliminary data from 144 cord blood transplantations at our institution over a 10-year period through 2013 suggests higher readmission rates for both the 30-day and day +100 time points compared with those reported in this analysis, at 33.6% and 46.7%, respectively [24].

Defining preventable readmissions in the transplantation population is challenging. The procedure is associated with significant risk of serious and potentially fatal infections as well as GVHD, resulting in a lower threshold to readmit given the high-risk nature of the population. The occurrence of infection during the index transplantation admission is a factor that can potentially be used from both a preventative and predictive standpoint. Stringent infection control measures, such as adherence to hand hygiene, isolation precautions, and rigorous line care may help prevent some of the infections that result in readmissions. If patients are diagnosed with an infection during their transplantation admission, additional resources could be devoted to ensuring a safe discharge plan and close follow-up. The occurrence of acute GVHD during the index transplantation admission could be treated similarly. Although the studied sociodemographic and disease-related factors found to be significant predictors of readmission are largely not preventable, they can be used to help further identify higher risk patients who would benefit from additional resources, such as more frequent appointments, discharge phone calls, or improved communication with local physicians to decrease the need for hospital admission.

The changing landscape of medicine has resulted in a growing focus on quality of care. Although readmissions are costly and are felt to represent failure of care transition, it must be recognized that quality metrics cannot be uniformly generalized to all populations. There is an overall paucity of data on the readmission profiles of oncology patients. The allogeneic transplantation population is a particularly unique subset of patients within oncology and further research is needed to better understand this group's readmission profile.

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REFERENCES

1. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418-1428.
2. Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. *Circ Heart Fail*. 2010;3:97-103.
3. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA*. 2010;303:1716-1722.
4. Lindenauer PK, Bernheim SM, Grady JN, et al. The performance of US hospitals as reflected in risk-standardized 30-day mortality and readmission rates for Medicare beneficiaries with pneumonia. *J Hosp Med*. 2010;5:E12-18.
5. Keenan PS, Normand SL, Lin Z, et al. An administrative claims measure suitable for profiling hospital performance on the basis of 30-day all-cause readmission rates among patients with heart failure. *Circ Cardiovasc Qual Outcomes*. 2008;1:29-37.
6. Mulvey GK, Wang Y, Lin Z, et al. Mortality and readmission for patients with heart failure among U.S. News & World Report's top heart hospitals. *Circ Cardiovasc Qual Outcomes*. 2009;2:558-565.
7. Krumholz HM, Merrill AR, Schone EM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. *Circ Cardiovasc Qual Outcomes*. 2009;2:407-413.
8. Joynt KE, Orav EJ, Jha AK. Thirty-day readmission rates for Medicare beneficiaries by race and site of care. *JAMA*. 2011;305:675-681.
9. Readmissions Reduction Program [Internet]. Centers for Medicare & Medicaid Services. Available at: http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html. Accessed January 5, 2014.
10. Stranges E, Russo A, Friedman B. Statistical Brief #82: Procedures with the Most Rapidly Increasing Hospital Costs, 2004–2007 [Internet]. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb82.jsp. Accessed January 5, 2014.
11. Pasquini MC, Wang Z. *Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides* [Internet]. Available at: http://www.cibmtr.org; 2012. Accessed January 5, 2014.
12. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA*. 2010;303:1617-1624.
13. Majhail NS, Murphy EA, Omondi NA, et al. Allogeneic transplant physician and center capacity in the united states. *Biol Blood Marrow Transplant*. 2011;17:956-961.
14. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628-1633.
15. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120:905-913.
16. Przepiorka D, Weisdorf D, Martin P, et al. 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825-828.
17. Cox D. *Analysis of Binary Data*. London: Methuen; 1970.
18. Kruskal W. A nonparametric test for the several sample problem. *Ann Math Statist*. 1952;23:525-540.
19. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
20. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc [A]*. 1972;135:185-206.
21. Cox D. Regression models and lifetables. *J R Stat Soc [B]*. 1972;34:187-220.
22. Bejanyan N, Bolwell BJ, Lazaryan A, et al. Risk factors for 30-day hospital readmission following myeloablative allogeneic hematopoietic cell transplantation (allo-HCT). *Biol Blood Marrow Transplant*. 2012;18:874-880.
23. Rauenzahn S, Truong Q, Cumpston A, et al. Predictors and impact of thirty-day readmission on patient outcomes and health care costs after reduced-toxicity conditioning allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:415-420.
24. Crombie J, Spring L, Li S, Soiffer R, et al. Readmissions following umbilical cord blood stem cell transplantation [abstract]. In: ASCO Quality Care Symposium; 2014 Oct 17-18; Boston, MA. *J Clin Oncol*. 2014;32(suppl 30). abstr 272.